Urea Cycle

Introduction

The urea cycle is very much like sphingolipids in the sense that their vocabularies are filled with long, difficult words unlike what we've learned so far in metabolism. The urea cycle is certainly "high-yield for life" (as in, without it you would die), but protein metabolism starts to wane on the board-relevance utility scale. We are not going to go deep into regulation or mechanisms, just walk through the urea cycle enzymes and the two clinically relevant enzyme deficiencies, and show how well the steps are named. This isn't a hard cycle, and you can get some free wins on the pattern recognition of presentation and matching of names-of-enzymes to names-of-intermediates.

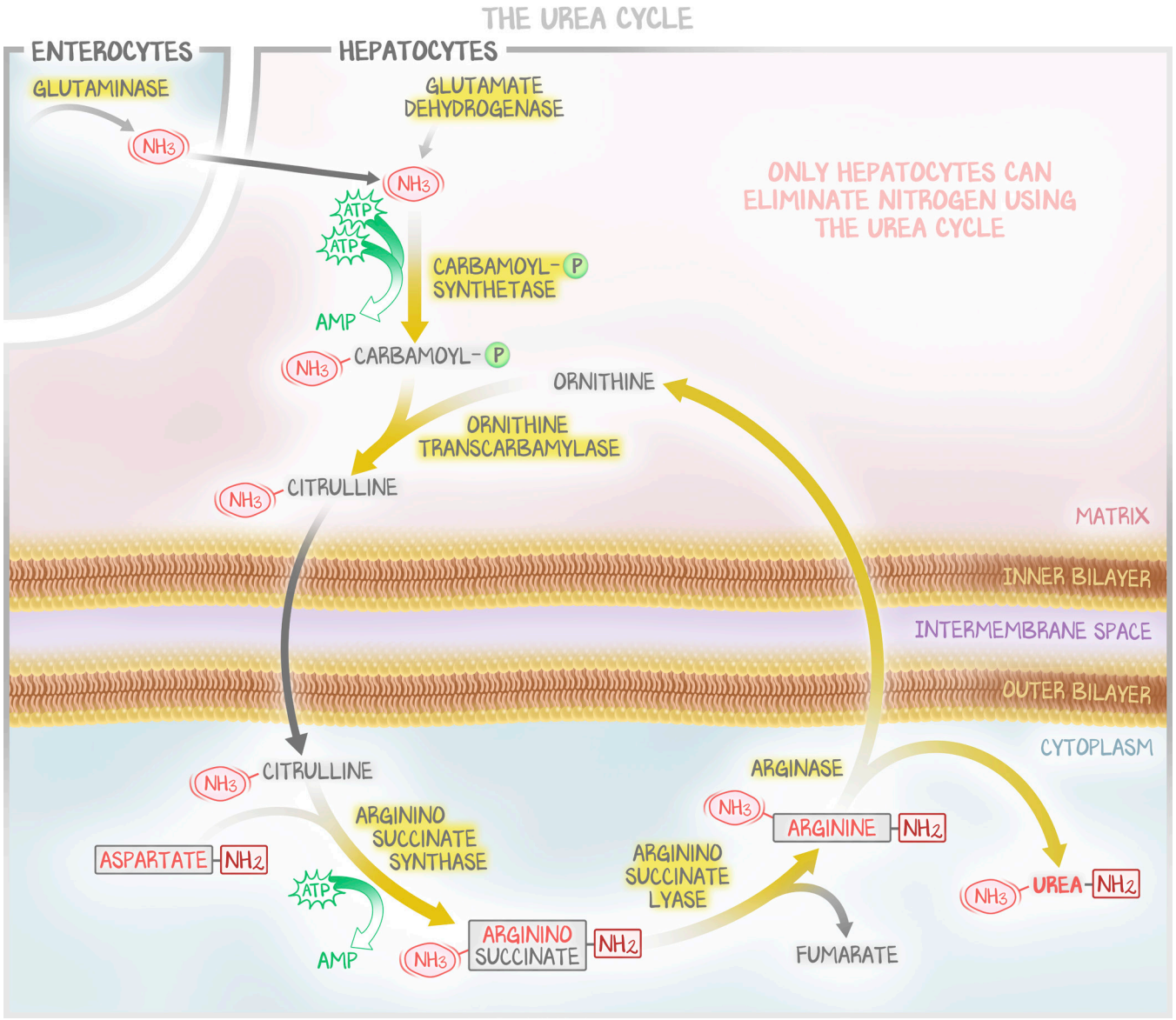

Figure 19.1: The Urea Cycle
Energy states, nitrogen sources, and final elimination of excess nitrogen as urea.

Entering the Cycle

Enterocyte glutaminase degrades glutamine to glutamate, releasing free NH_3 into portal circulation. Hepatocyte glutamate dehydrogenase liberates the amino group from glutamate, forming a free NH_3. This free NH_3 is processed starting in the mitochondria. **NH_3** is synthesized into **carbamoyl-P**. The enzyme that synthesizes carbamoyl-P is **carbamoyl-P synthetase I**. This is a high-energy step, requiring **2 ATP** to charge the NH_3 with carbon. This is the only step in nitrogen metabolism that is **not in the cycle itself**. We have it labeled as step 0 of the cycle. Since we do not cover purine and pyrmidine metabolism in detail, there is no other carbamoyl-P synthetase you need to know about, but for thoroughness, there is a cytoplasmic type II for purine metabolism.

Later in the cycle an aspartate will come from aspartate aminotransferase from the liver.

The Cycle

The **cycle begins in the mitochondria**. Carbamoyl-P was just made. At the end of the cycle is mitochondrial **ornithine**. Ornithine is an amino acid that we have no codon for. It is built. Because this is a cycle, the **intermediates are neither consumed nor destroyed**, only cycled. Anything along the cycle itself is regenerated with each turn of the cycle. Anything coming into or out from the main loop of the cycle is created or consumed.

Ornithine combines with **carbamoyl-P** in the mitochondria to become **citrulline**. The enzyme that does this is ornithine-trans-carbamoyl-ase. It has the words **ornithine** and **carbamoyl-P** in it, the same as both substrates. Citrulline moves to the cytoplasm.

Citrulline is synthesized into **argininosuccinate**. Citrulline already has a nitrogen from the original step (NH_3 from the mitochondria). In this step, where argininosuccinate is synthesized by **argininosuccinate synthetase**, more **ATP** is used and the **entire aspartate** from aspartate aminotransferase is glued to citrulline, making the argininosuccinate. That means a nitrogen from the mitochondria (NH_3) is combined with a nitrogen from the cytoplasm (aspartate), having **two extra nitrogens**. These are the nitrogens that will be released as urea.

Argininosuccinate is broken down into **arginine** and **fumarate**. Argininosuccinate is broken down by **argininosuccinate lyase**. Fumarate goes off to enter the Krebs, become glucose, etc. **Arginine** is metabolized by **arginase** to regenerate ornithine and **release urea**.

Deficiencies

Only deficiencies of the mitochondrial enzymes present clinically. Cytoplasmic deficiencies are nonviable. If a baby is born with a deficiency in nitrogen metabolism, nitrogen will accumulate. This means that all forms of nitrogen will back up and accumulate.

NH_3 increases in the blood (hyperammonemia). Because NH_3 can cross the blood-brain barrier, it does as it accumulates, forming NH_4^+. NH_4^+ is both osmotically active and toxic to the brain. This will cause **encephalopathy**, followed by **cerebral edema**. Cerebral swelling is bad, and babies have a pressure valve of the skull, so you will see **bulging fontanelles**. The patient progresses from a poor Apgar score at birth to **lethargy**, **coma**, and **death**. However, there may be no sign of nitrogen accumulation for the first 24 hours, therefore a **day 1 well-baby check may be near normal**.

Glutamine increases simply because it becomes the **only mechanism for nitrogen metabolism**. So the levels of glutamine in the serum rise. But remember, it was usually a very minor mechanism. It cannot pick up the slack of the loss of the urea cycle, and nitrogen accumulates.

BUN decreases. Since **urea** cannot be made and BUN is blood-urea-nitrogen, and since the liver is making less urea, and since the kidneys are clearing whatever urea they get, the blood-urea-nitrogen decreases. Do not be fooled, the blood nitrogen is going up—there is hyperammonemia. However, the amount of it that is urea is less. The BMP, the blood test for kidney function, looks at **urea-nitrogen**.

Sounds bad for baby. And notice I haven't said anything about enzymes, disease names, or how to tell them apart. And because this next part is the only difference between the two syndromes, and urea cycle syndromes are a grand total of two, you had better believe the thing that comes next is super-board-relevant. **OTC-ase deficiency has orotic aciduria; carbamoyl-P-synthetase I deficiency does not.**

Carbamoyl-P-synthetase I deficiency has nothing to do with pyrimidines. Therefore, in the presence of hyperammonemia in a newborn infant, with coma, lethargy, and cerebral edema, carbamoyl-P synthetase I deficiency is apparent by the **absence of orotic** aciduria. What the hell is orotic aciduria? Orotic acid is an intermediate of pyrimidine synthesis. Because it's an acid, it makes the urine acidic. Carbamoyl-P synthetase I **does not have acidic urine** and there is **no orotic acid** in the urine. This is also **autosomal recessive**, so if they give a gender and it's female, pick this.

Ornithine-trans-carbamoyl-ase deficiency has a lot to do with pyrimidines. Therefore, in the presence of hyperammonemia in a newborn infant, with coma, lethargy, and cerebral edema, OTC-ase deficiency is apparent by the **presence of orotic aciduria**. Be careful here. Absence of orotic aciduria means that it IS carbamoyl-P synthetase. The presence of orotic aciduria on its own means it is not carbamoyl-P synthetase I deficiency. Orotic acid gets into the urine in pyrimidine metabolism disorders beyond OTC-ase deficiency. But at that point, honestly, "if orotic aciduria, pick OTC-ase deficiency."

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Carbamoyl-P is the substrate of OTC-ase, and will accumulate in OTC-ase deficiency, because it is not being used in the urea cycle. Carbamoyl-P is also the substrate for transcarbamoylase in pyrimidine synthesis, which, because it accumulates, will favor the reaction of pyrimidine synthesis. In carbamoyl-P synthestase I deficiency, carbamoyl-P cannot accumulate, and so the transcarbamoylase of pyrimidine synthesis cannot have extra substrate, so no orotic aciduria.